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**WO 01/18073 A1**

(54) Title: PROCESS FOR REDUCING COHESIVENESS OF POLYALLYLAMINE POLYMER GELS DURING DRYING

(57) Abstract: Disclosed is a cross-linked polyallylamine polymer composition having reduced cohesiveness, a process for producing a cross-linked polyallylamine polymer having reduced cohesiveness from an aqueous solution of a washed cross-linked polyallylamine polymer treated with a surfactant and to cross-linked polyallylamine polymer compositions produced thereby.

# PROCESS FOR REDUCING COHESIVENESS OF POLYALLYLAMINE POLYMER GELS DURING DRYING

5                    This invention relates to a process for producing a polyallylamine polymer gel having reduced cohesiveness during drying and to cross-linked polyallylamine polymer gel compositions produced thereby.

                  Cross-linked polyallylamine polymers have found many therapeutic applications. See for example, WO 98/57652, JP 07309766-A and USP 5,618,530,  
10 5,679,717, 5,693,675 and 5,607,669 for reducing blood cholesterol levels by reducing reabsorption of bile acids, USP 5,702,696 for decreasing the absorption of dietary iron from the gastrointestinal track, and WO 96/21454 and USP 5,496,545 for removing phosphate from the gastrointestinal track. Further, JP 05244915 discloses the use of cross-linked polyamine polymers as food preservatives.

15                    Methods to produce cross-linked polyamine polymers are known. See for example, the references cited above and USP 4,605,701, DE 4227019 A1 and EP 732352 A1. These references disclose cross-linking the polyallylamine polymer by reacting the polymer with a suitable cross-linking agent in aqueous caustic solution or an aqueous caustic solution and immiscible solvent mixture.

20                    The existing methods to produce cross-linked polyamine polymers create difficult and costly handling and cleanup procedures, especially in an industrial production process. In all cases, once the polymer gel is dried to a certain volatile content (dependent on temperature), it becomes extremely cohesive and sticks to itself. This cohesive phase results in a significantly increased power requirement to agitate the polymer and a  
25 decreased heat transfer efficiency from the heated dryer shell. The present invention addresses these problems and gives a more practical solution to them.

                  The present invention is directed to a process for producing a cross-linked polyallylamine polymer gel having reduced cohesiveness during drying comprising the steps of reacting an aqueous solution of a polyallylamine polymer with a multifunctional cross-  
30 linking agent, preferably epichlorohydrin, to give a cross-linked polyallylamine polymer.

                  One embodiment of the present invention comprises the step of washing the cross-linked polyallylamine polymer with an alcohol or alcohol/water solution.

                  In a further embodiment, the present invention comprises the step of drying the cross-linked polyallylamine polymer.

In yet a further embodiment, the present invention involves the use of a reactor designed for high viscosity processing, preferably a LIST reactor, in the cross-linking and/or drying steps.

In yet a further embodiment, the present invention involves compositions of cross-linked polyallylamine polymers produced by the foregoing process.

The present invention provides a process for producing a cross-linked, water-insoluble but swellable polyallylamine polymer that has decreased cohesiveness during drying. The process comprises subjecting a portion of the amino groups present in an aqueous solution of polyallylamine polymer to a cross-linking reaction with a compound having, in its molecule, at least two functional groups reactive with primary amino groups, as well as providing said cross-linked polyallylamine polymers.

The polyallylamine acid salt polymer used in the present invention is well known from references cited above and USP 4,528,347. Generally, monoallylamine is polymerized as a monomer inorganic acid salt (for example, hydrochloride, sulfate, etc.) of monoallylamine in the presence of an azo type radical initiator. The polyallylamine acid salt polymer used in the invention typically has a weight average molecular weight ("MW<sub>w</sub>") greater than 2,000 daltons and more preferably greater than 20,000 daltons. The polyallylamine polymer used in the invention typically has a MW<sub>w</sub> less than or equal to 200,000 daltons and more preferably less than or equal to 100,000 daltons. Polyallylamine hydrochloride polymer, the polymerization product from the hydrochloric acid salt of monoallylamine, is a preferred polyallylamine acid salt polymer.

Preferably, the polyallylamine acid salt polymer is neutralized prior to cross-linking. The neutralized polyallylamine polymer is sometimes referred to as polyallylamine polymer. The aqueous solution of polyallylamine polymer used in the invention is prepared by dissolving a polyallylamine acid salt polymer (obtained by the process described above) into water or other suitable solvent. Neutralization can be accomplished with any suitable base such as ammonium hydroxide, preferably sodium hydroxide, by ion exchange, electrodeionization or by other suitable methods.

Neutralization of an aqueous solution of polyallylamine hydrochloride polymer by a suitable base (for example, lithium hydroxide, potassium hydroxide, sodium hydroxide, etc.) provides an aqueous solution of polyallylamine polymer with high levels of salt (for example, sodium chloride). However, means to remove salt, for example, ion exchange, dialysis, nanofiltration or ultrafiltration may be used to provide the aqueous solution of polyallylamine polymer of the present invention.

Preferably, reducing the level of salt in polyallylamine polymer to provide a reduced salt polyallylamine polymer is done by ultrafiltration. Ultrafiltration is a pressure driven filtration separation occurring on a molecular scale and is well known in the art. Typically, a process fluid containing dissolved and/or suspended material contacts one side of a porous membrane. A pressure gradient is applied across the membrane. The liquid, including small dissolved molecules (for example, unreacted allylamine and low molecular weight polyallylamine polymer) and ions (for example, the salt) are forced through the pores. Sieving retains colloids, suspended solids, and large dissolved molecules (for example, the polyallylamine polymer). A good discussion of ultrafiltration is contained in *Encyclopedia of Polymer Science and Engineering*, 1988, Volume 17, pp. 75-107.

A complete neutralization of the polyallylamine acid salt polymer prior to cross-linking is not always necessary. Depending on its intended use, a partial neutralization is also allowable and often desirable to give the desired level of cross-linking, pH, properties and efficacy for the cross-linked polyallylamine polymer. Preferably, the polyallylamine acid salt polymer is neutralized to a point where at least 50 percent, more preferably at least 60 percent, even more preferably at least 65 percent, even more preferably at least 70 percent, and most preferably at least 71 percent of the amino groups in the polyallylamine acid salt polymer are neutralized. Preferably, the polyallylamine acid salt polymer is neutralized whereby 100 percent, more preferably no more than 90 percent, more preferably no more than 80 percent, even more preferably no more than 75 percent, even more preferably no more than 73 percent, and most preferably 72 percent of the amino groups in the polyallylamine acid salt polymer are neutralized.

Preferably, the aqueous solution of polyallylamine polymer is concentrated following neutralization and prior to cross-linking by any known means in the art such as concentrative ultrafiltration or flash evaporation under vacuum at elevated temperatures. Preferably the reduced salt, aqueous solution contains at least 1.5 milliequivalents polyallylamine polymer per gram of solution ("meq/g"), more preferably at least 2.0 meq/g, even more preferably at least 2.5 meq/g, even more preferably at least 3.0 meq/g, even more preferably at least 3.5 meq/g, even more preferably at least 4.0 meq/g, even most preferably at least 4.5 meq/g polyallylamine polymer. Preferably the reduced salt, aqueous solution contains less than or equal to 9.0 meq polyallylamine polymer per gram of solution, more preferably less than or equal to 8.5 meq/g, more preferably less than or equal to 8.0 meq/g, more preferably less than or equal to 7.5 meq/g, more preferably less than or equal to 7.0 meq/g, more preferably less than or equal to 6.5 meq/g, and most preferably less than or equal to 6.0 meq/g polyallylamine polymer.

The cross-linking agent and aqueous solution of the polyallylamine, preferably concentrated aqueous solution of the polyallylamine are mixed together, preferably at room temperature and allowed to react. Examples of suitable cross-linking agents include acryloyl chloride, epichlorohydrin, butanedioldiglycidyl ether, preferably 1,4 butanedioldiglycidyl ether, 5 ethanedioldiglycidyl ether preferably 1,2 ethanedioldiglycidyl ether, 1,3-dichloropropane, 1,2-dichloroethane, 1,3-dibromopropane, 1,2-dibromoethane, succinyl dichloride, dimethylsuccinate, toluene diisocyanate, and pyromellitic dianhydride. A preferred cross-linking agent is epichlorohydrin because of its low cost. Epichlorohydrin is also advantageous because of its low molecular weight and hydrophilic nature, maintaining the 10 water swellability and phosphate-binding efficacy of the resulting polyallylamine polymer gel.

When used in therapeutic applications, such as sequestration of bile acids or the binding of phosphate in the gastrointestinal tract, the level of cross-linking makes the polymer insoluble and substantially resistant to absorption and degradation. Preferably, the cross-linking agent is present in an amount from 0.1 weight percent, more preferably from 15 0.5 weight percent, even more preferably from 1.0 weight percent, even more preferably from 2.0 weight percent and most preferably from 5.0 weight percent, weight percent based on the combined weight of (partially) neutralized polyallylamine polymer and cross-linking agent. Typically, the cross-linking agent is present in an amount less than or equal to 75 weight percent, more preferably in an amount less than or equal to 50 weight percent, even 20 more preferably in an amount less than or equal to 25 weight percent, even more preferably in an amount less than or equal to 20 weight percent and most preferably in an amount less than or equal to 10 weight percent, based on the combined weight of (partially) neutralized polyallylamine polymer and cross-linking agent .

The cross-linking reaction can be run in any suitable vessel or reactor. A 25 preferred reactor is one in which the reaction can be run batch-wise or in a continuous fashion. More preferred is a reactor designed for high viscosity processing which has agitation means capable of mixing the reactants prior to gelation and breaking the gel into small pieces or crumb after gelation. An example of a preferred reactor designed for high viscosity processing is a LIST-DISCOTHERM B manufactured by LIST Inc. 42 Nagog Park, 30 Acton, MA 01720, USA.

The LIST-DISCOTHERM B can be supplied for batch or continuous operation. It is particularly useful for thermal processes such as drying or reactions, where mixing or kneading is necessary to process viscous, pasty, crusting or gelatinous materials such as cross-linked polyallylamine polymer.

The basic unit consists of a horizontal, cylindrical housing, and a concentric agitator shaft with disc elements perpendicular to the axis carrying peripheral mixing/kneading bars. Stationary hook-shaped bars set in the shell interact with, and clean, the shaft and disc elements as they rotate. Shell, shaft, and disc elements, all of which contribute to heat transfer can be heated or cooled. The unit generally operates with a fill level of 60 to 75 percent reactor capacity. Typical shaft speeds range from 5 to 100 rotations per minute ("rpm") with high installed torque. The combined effect of the intensive mixing and kneading action and the self cleaning of the heat exchange surfaces results in high heat and mass transfer rates. In batch units the mixing bars are arranged to perform optional mixing. For continuous operation, the arrangement of the internal geometry provides a forward plug flow movement of the material. However, the axial conveying rate is nearly independent of agitator rotation speed, making it possible to operate at high agitator rotation speeds optimizing heat and mass transfer. Furthermore, the positioning of the disc elements enables the processing of liquid feed stocks directly through to a solid free flowing material without recycling of dry product. The unique design of the LIST reactor eliminates the formation of a single, continuous, congealed mass. As gelation occurs, the self-wiping concentric agitator shaft and disc elements create easy to handle clumps of gel.

The mixture of cross-linking agent and the reduced salt, aqueous solution of the polyallylamine is agitated, preferably between 60 to 100 rpm, more preferably 80 rpm until the mixture has gelled. Once the mixture has gelled, the reaction is allowed to continue, a process sometimes referred to as cure. During curing, the rate of agitation is decreased, made intermittent or discontinued to minimize shear degradation of the cross-linked polymer, preferably agitation is continuous and/or intermittent (on/off) at 20 rpm. Preferably during curing the reaction temperature is increased, for example to between 70 to 80°C, for an extended period, for example from 5 to 20 hours.

Unreacted or minimally reacted starting materials are sometimes referred to as soluble oligomers. Shear degraded cross-linked polyallylamine polymer is another source of soluble oligomers. Cross-linked polyallylamine polymer is particularly susceptible to shear degradation resulting from the arduous clean-up procedures required to remove salt from the polymer. Soluble oligomers are undesirable in the final cross-linked polyallylamine polymer. Preferably, the cross-linked polyallylamine polymer is washed to remove undesirable soluble oligomers. Any medium may be used as long as the cross-linked polyallylamine is not soluble in it while the soluble oligomers are soluble in the medium. Preferably, water, one or more alcohols such as methanol, ethanol, propanol, isopropyl alcohol, and mixtures of one or more of these are used as the wash medium. The cross-linked polyallylamine polymer

may be washed one or more times to reduce the soluble oligomers to a desired level. If soluble oligomers are present in the final cross-linked polyallylamine polymer, preferably they are present in an amount less than 1 weight percent, more preferably in an amount less than 0.8 weight percent, more preferably in an amount less than 0.6 weight percent, and most preferably in an amount less than 0.5 weight percent based on the weight of the cross-linked polyallylamine polymer.

The cross-linked polyallylamine polymer is then separated from the aqueous solution and dried by any suitable means. For example, the cross-linked polyallylamine polymer can be separated from the aqueous solution by filtration or centrifugation then dried in a vacuum oven or a LIST dryer. After filtering to remove the free liquid, the gel enters a dryer at a concentration of 5 to 60 percent solids. Preferably, the cross-linked polyallylamine polymer is dried under vacuum at a temperature less than 80°C. The dried cross-linked polyallylamine polymer is preferably ground by any suitable method, for example mortar and pestle, a Retsch Mill, or a FitzMill.

During the above drying step, once the gel is dried to a certain volatile content (dependent on temperature), it becomes extremely cohesive and sticks to itself. This cohesive phase results in significantly increased power requirements necessary to rotate the agitator and a decreased heat transfer efficiency from the heated dryer shell. As a result of these problems, drying times become extended and significant decreases in productivity are realized. The addition of low levels of surfactant to the wet gel before drying decreases the cohesiveness of the gel. Accordingly, important productivity advantages, including faster drying rate and the ability to increase dryer loading to full capacity without resulting in physical damage to the dryer are realized. Preferably, a surfactant such as MICRO-90 concentrated cleaning solution at concentrations of from 1600 to 2500 parts per million (ppm) based on dry product weight or stearic acid at a concentration of from 10 to 1000 ppm based on dry product weight is added to the wet gel. More preferably, stearic acid is added in an amount of from 75 to 125 ppm based on dry product weight to the wet gel. Most preferably, stearic acid in amount of 100 ppm based on dry product weight is added to the wet gel. MICRO-90 is a mixture of four different ingredients in water, including both anionic and nonionic surfactants. Specifically, MICRO-90 comprises a mixture of glycine, N,N'-1,2-ethanediylbis-N-(carboxymethyl)-, tetrasodium salt in a concentration of less than 20 percent; benzenesulfonic acid dimethyl-, ammonium salt in a concentration of less than 20 percent; benzenesulfonic acid dodecyl-, compounded with 2,2',2"-nitrilotris (ethanol) in a concentration of less than 20 percent; and poly(oxy-1,2-ethanediyl), alpha-(undecyl)-omega-hydroxy in a concentration of less than 20 percent. The remainder of the

mixture is comprised of water. MICRO-90 is available commercially from the manufacturer, International Products Corporation, Burlington, NJ, USA. Stearic acid is an anionic surfactant that is preferably dissolved in isopropanol before addition to the dryer.

To illustrate the practice of this invention, examples of preferred embodiments are set forth below. However, these examples do not in any manner restrict the scope of this invention.

### EXAMPLES

Cross-linked polymers were prepared according to the following procedure.

First, an aqueous solution of a polyallylamine polymer was reacted with an epichlorohydrin cross-linking agent to give a cross-linked polyallylamine polymer. The polyallylamine polymers used in the Examples comprised aqueous solutions of poly(allylamine hydrochloride) having a MW<sub>w</sub> of 17,000 daltons. The polyallylamine polymers are available commercially from Aldrich Chemical Company, Inc., 1001 West Saint Paul Avenue, Milwaukee, WI, USA. The aqueous solution of cross-linked polyallylamine polymer was then washed with an isopropanol/water solution. These "wet" cross-linked polyallylamine polymers were then used to test the effectiveness of adding a surfactant to the wet polymer before drying.

Drying was performed in a LIST DISCOTHERM B 6.3 liter batch processor.

The core of the LIST is a 6" horizontal cylindrical shell in which rotates a shaft fitted with disc elements and mixing bars. Stationary counter hooks on the inside of the shell interact with the rotating bars and discs providing a mixing / kneading action which eliminates product buildup and results in a self-cleaning system. A 10 horsepower hydraulic power unit drove the agitator. Dowtherm J heat transfer fluid was used to heat the hollow shell and shaft, and a 3 horsepower Siemen & Hirsch liquid-ring vacuum pump was used to control the system vacuum level.

#### Example 1

Isopropanol-wet cross-linked polyallylamine polymer was produced following the procedure described above. After flushing the dryer with hot water for several hours, the gel was loaded into the dryer. While agitating at 20 rpm the gel was dried at a jacket temperature of 80° and a vacuum level of 50mm Hg for 3 hours and unloaded.



Example 2

Isopropanol-wet cross-linked polyallylamine polymer was produced following the procedure described above. The dryer was thoroughly cleaned with hot water for several hours. 1.0g of MICRO-90 was diluted in 20 g of deionized (DI) water and added to the LIST before loading the gel. While agitating at 20 rpm the gel was dried at a jacket temperature of 80° and a vacuum level of 50mm Hg for 3 hours and unloaded.

Example 3

Isopropanol-wet cross-linked polyallylamine polymer was produced following the procedure described above. After flushing the dryer with hot water for several hours, the gel was loaded into the dryer. While agitating at 20 rpm the gel was dried for 5 hours and unloaded. The jacket temperature was set to 60°C for 1 hour, then 70°C for 1 hour, and then 80°C for 3 hours. The vacuum level was set to 200 mm Hg for 2 hours and then 100 mm Hg for 3 hours.

Example 4

Isopropanol-wet cross-linked polyallylamine polymer was produced following the procedure described above. The dryer was flushed with hot water for several hours. 0.035 g of solid stearic acid was dissolved in 10 g of isopropanol and added to the LIST before loading the gel. While agitating at 20 rpm the gel was dried for 5 hours and unloaded. The jacket temperature was set to 60°C for 1 hour, then 70°C for 1 hour, and then 80°C for 3 hours. The vacuum level was set to 200 mm Hg for 2 hours and then 100 mm Hg for 3 hours.

Table 1 of Results:

| Example # | Gel Loaded ( g ) | % solids | Surfactant added     | Cohesive | Max Agitator Pressure (psi) |
|-----------|------------------|----------|----------------------|----------|-----------------------------|
| 1         | 765              | 48.2     | None                 | yes      | 250                         |
| 2         | 770              | 48.2     | 1.0 g MICRO-90       | no       | 50                          |
| 3         | 891              | 45.1     | None                 | yes      | 280                         |
| 4         | 906              | 45.1     | 0.035 g stearic acid | no       | 45                          |

The cohesive phase in examples 2 and 4 was confirmed by visual observation through a sight-glass and by the increase in maximum agitator hydraulic pressure for the untreated samples.

As can be seen, addition of small amounts of surfactant to the wet gel achieved remarkable decreases in maximum agitator pressure. As a result, power

requirements for the dryer were reduced and productivity advantages such as increasing dryer loading to full capacity become possible.

The dried gel from examples 3 and 4 was screened with successively finer mesh sieves using an Allen-Bradley L3 series Sonic Sifter, available commercially from Thomas Scientific, 99 High Hill Road @I-295, PO Box 99, Swedesboro, New Jersey 08085 USA at an amplitude setting of 7 for 10 minutes. The results are summarized in Table 2 below. The mesh sizes indicated in Table 2 are equivalent to the alternate sieve designation sizes described in Table 21-6 of *Perry's Chemical Engineers' Handbook*, 6<sup>th</sup> Ed., 1984, p. 21-15. According to that reference, an 18 mesh sieve would comprise a series of 1mm openings, with higher mesh sizes designating smaller openings, all the way down to a 149 micron opening for the 100 mesh designation.

As can be seen, agglomeration of the gel into bigger particles that increase the incidence of clogging and slow production is most obvious during the first separation cut at 18 mesh. 76.58 percent of all particles were retained on the untreated side, as opposed to 28.7 percent of all particles on the surfactant treated side. At the 40 mesh level, a cumulative 96.24 percent of all particles were retained on the untreated side, compared to 57.3 percent of all particles on the surfactant treated side. These retention levels demonstrate that the surfactant treated gel produces a substantially lower number of large particles, resulting in reduced cohesiveness of the dried gel.

Table 2:

| Screen<br>(mesh) | % Retained |        |
|------------------|------------|--------|
|                  | Ex. #3     | Ex. #4 |
| 18               | 76.58%     | 28.7%  |
| 40               | 19.66%     | 28.6%  |
| 50               | 3.07%      | 17.2%  |
| 60               | 0.00%      | 8.6%   |
| 70               | 0.01%      | 4.4%   |
| 100              | 0.34%      | 12.1%  |
| Fines            | 0.35%      | 0.5%   |

The following analytical procedures were run on the cross-linked polyallylamine polymers of Examples 1-4:

Swell is determined by placing 0.1g of dry polyallylamine polymer into a two piece centrifuge tube and stirring with 5 ml of water for two hours. Thereafter the slurry is centrifuged and the resultant gel mass weighed to yield swell:

Swell = (mass final-mass initial)/mass initial.

The centrifugate (extract) from the swell is used for the determination of both soluble oligomers and sodium chloride concentration.

Soluble oligomers (SO) are determined by a modification of the method published by McLean (J. D. McLean, V. A. Stenger, R. E. Reim, M. W. Long and T. A. Hiller, Anal. Chem., 50, 1309 (1978) in which a portion of the extract is derivatized with formaldehyde and then determined polarographically by the reduction of the Schiff's base and compared to a spiked sample.

Phosphate binding capacity ("PO<sub>4</sub>") is determined by a method similar to that published in USP 5,496,545 with the exception that detection was by chromatographic rather than spectrophotometric techniques.

Analytical results:

| Example | Phosphate Binding | Swell Index | Soluble Oligomers |
|---------|-------------------|-------------|-------------------|
| 1       | 5.69              | 7.06        | 1106              |
| 2       | 5.56              | 6.87        | 1067              |
| 3       | 5.64              | 7.05        | 234               |
| 4       | 5.54              | 7.27        | 197               |

As can be seen, the levels of soluble oligomers were unchanged as a result of the addition of surfactants to the wet gel. Further, the water swellability and phosphate-binding efficacy of the resulting polyallylamine polymer gel were also maintained. This demonstrates that addition of surfactants to the wet polymer gel has no negative impact on the functional characteristics of the resulting product.

## WHAT IS CLAIMED IS:

1. A process for producing a cross-linked polyallylamine polymer having reduced cohesiveness comprising the steps of:

- 5 (a) reacting an aqueous solution of a polyallylamine polymer with a multifunctional cross-linking agent to give a cross-linked polyallylamine polymer;
- (b) washing the aqueous solution of cross-linked polyallylamine polymer with an alcohol/water solution;
- 10 (c) adding a cohesion-reducing amount of surfactant to the washed cross-linked polyallylamine polymer;
- (d) drying the cross-linked polyallylamine polymer;
- (e) grinding and sieving the cross-linked polyallylamine polymer; and
- (f) isolating the cross-linked polyallylamine polymer.

15

2. The process of Claim 1 further comprising the step of partially neutralizing the aqueous solution of polyallylamine hydrochloride polymer by ion exchange or electrodeionization before reacting the aqueous solution of a polyallylamine polymer with a multifunctional cross-linking agent.

20

3. The process of Claim 2 further comprising the step of nanofiltering or ultrafiltering the aqueous solution of polyallylamine polymer after partially neutralizing the aqueous solution of polyallylamine hydrochloride polymer by ion exchange or electrodeionization.

25

4. The process of Claim 1 further comprising the steps of:

- (a) partially neutralizing the aqueous solution of polyallylamine hydrochloride polymer with a suitable base; and
- 30 (b) ultrafiltering the partially neutralized, aqueous solution of polyallylamine polymer to give the aqueous solution of polyallylamine polymer.

30

5. The process of Claim 4 wherein the base is sodium hydroxide.

6. The process of Claim 1 further comprising the step of concentrating the aqueous solution of polyallylamine polymer.

35

7. The process of Claim 1 wherein the step of drying the cross-linked polyallylamine polymer is carried out under reduced pressure.

5 8. The process of Claim 1 wherein the reaction occurs in a reactor designed for high viscosity processing.

9. The process of Claim 8 wherein the reactor is a LIST reactor.

10 10. The process of Claim 1 wherein the cross-linking agent is present in an amount from 0.1 to 75 weight percent based on the combined weight of polymer and cross-linking agent.

11. The process of Claim 1 wherein the cross-linking agent is present in an  
15 amount from 2 to 20 weight percent based on the combined weight of polymer and cross-linking agent.

12. The process of Claim 1 wherein the cross-linking agent is acrylol  
chloride, epichlorohydrin, butanedioldiglycidyl ether, or ethanedioldiglycidyl ether.

20 13. The process of Claim 1 wherein the cross-linking agent is epichlorohydrin.

14. The process of Claim 1 wherein the alcohol is ethyl alcohol, n-propanol,  
25 or isopropyl alcohol.

15. The process of Claim 1 wherein the alcohol is isopropyl alcohol.

16. The process of Claim 1 wherein the surfactant is stearic acid.

30 17. The process of Claim 16 wherein the stearic acid is added in an amount of from 10 to 1000 parts per million.

18. The process of Claim 17 wherein the stearic acid is added in an amount  
35 of from 75 to 125 parts per million.

19. The process of Claim 18 wherein the stearic acid is added in an amount of 100 parts per million.

5                   20. A cross-linked polyallylamine polymer composition having reduced cohesiveness.

                  21. A cross-linked polyallylamine polymer composition having reduced cohesiveness produced by adding a cohesion-reducing amount of surfactant to a washed  
10 cross-linked polyallylamine polymer prior to drying and grinding of said polyallylamine polymer.

# INTERNATIONAL SEARCH REPORT

|  |   |  |
|--|---|--|
| <b>A. CLASSIFICATION OF SUBJECT MATTER</b><br>IPC 7 C08F8/00 A61K31/785  |   | International Application No<br><b>PCT/US 00/23695</b> |
| According to International Patent Classification (IPC) or to both national classification and IPC  |   |  |
| <b>B. FIELDS SEARCHED</b><br>Minimum documentation searched (classification system followed by classification symbols)<br>IPC 7 C08F A61K  |   |  |
| Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  |   |  |
| Electronic data base consulted during the international search (name of data base and, where practical, search terms used)<br>PAJ, WPI Data, EPO-Internal  |   |  |
| <b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>  |   |  |
| Category *   | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No.                                  |
| A  | EP 0 143 328 A (NITTO BOSEKI CO., LTD.)<br>5 June 1985 (1985-06-05)<br>cited in the application<br>claims 1-4<br>---  | 1  |
| A  | EP 0 229 380 A (FREUND INDUSTRIAL CO., LTD.) 22 July 1987 (1987-07-22)<br>page 4, line 35 - line 55<br>page 5, line 10 - line 36; claims 1-12<br>---  | 1  |
| A  | DATABASE WPI<br>Section Ch, Week 9534<br>Derwent Publications Ltd., London, GB;<br>Class A14, AN 1989-011158<br>XP002155893<br>& JP 63 286405 A (NITTO BOSEKI CO., LTD.),<br>24 November 1988 (1988-11-24)<br>abstract<br>--- | 1  |
| -/--   |   |  |
| <input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.  |   |  |
| * Special categories of cited documents :<br><div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>*A* document defining the general state of the art which is not considered to be of particular relevance</p> <p>*E* earlier document but published on or after the international filing date</p> <p>*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>*O* document referring to an oral disclosure, use, exhibition or other means</p> <p>*P* document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>*Z* document member of the same patent family</p> </div> </div> |   |  |
| Date of the actual completion of the international search<br><br><div style="text-align: center;">19 December 2000</div>   | Date of mailing of the international search report<br><br><div style="text-align: center;">02/01/2001</div>   |  |
| Name and mailing address of the ISA<br>European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax (+31-70) 340-3016   | Authorized officer<br><br><div style="text-align: center;">Permentier, W</div>  |  |

# INTERNATIONAL SEARCH REPORT

Intern. Patent Application No

PCT/US 00/23695

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